REMARKS

Rejection of Claims 1, 11-13, 18, 22, 26, 31, 36, 40, 41, 46, 51, 55-57, 60, 73-76, 78, 80-83, 93-96 and 99-107 Under 35 U.S.C. § 103(a)

Claims 1, 8-13, 18, 22, 26, 31, 36, 40, 41, 46, 51, 55-60, 62-64, 73-83, 93-97 and 99-107 are rejected under 35 U.S.C. §103(a) as being unpatentable over Ponath *et al.* (WO 98/06248) in view of Gordon *et al.* (Reference AS5 of record) or Gordon *et al.* (Reference AT5 of record).

The Examiner maintains that Ponath *et al.* disclose treatment of ulcerative colitis with humanized LDP-02 antibody, wherein said antibody has the amino acid sequence recited in the claims. The Examiner further states that Ponath *et al.* disclose that the dosage and schedule of administration used would be determined using routine experimentation, that the antibody can be administered in multiple doses, and that the patient can additionally receive steroids or sulfasalazine or other immunosuppressive agents. The Examiner admits that Ponath *et al.* do not disclose the particular claimed administration protocols. (Office Action, pages 2-3).

The Examiner further maintains that the Gordon *et al.* references disclose that patients with inflammatory bowel disease or ulcerative colitis can be treated with a dose of 3 mg of humanized antibody against an α4 integrin, wherein said dosage is a starting point for future clinical studies. In the Examiner's opinion, a routineer would have started with the 3 mg/kg dosage disclosed by Gordon *et al.* and arrived at the claimed protocols using routine experimentation. (Office Action, page 3).

In response to Applicants' previous arguments in view of studies summarized by Feagan *et al.* (references AX5 and AY5 of record), the Examiner states that Feagan *et al.* disclose that it is unclear as to whether their antibody is actually preferable to the use of natalizumab for treatment of ulcerative colitis. (Office Action, page 5). The Examiner further states that the studies presented in the Fedyk *et al.* abstract P-0144 and Feagan *et al.* abstract P-0025 indicate there are other agents used to treat IBD in humans and the abstracts do not provide information regarding the use of the recited antibody in comparison to other treatments for IBD. The Examiner also states that Fedyk *et al.* (Reference AZ5 of record) appears to use dosages that are outside those recited in the claims under consideration. (Office Action, page 6).

Applicants respectfully disagree. Although some scientists might have a desire to improve upon what is already generally known, one of ordinary skill in the art would not

consider the dosage of an unrelated antibody as a starting point for which to begin testing a different antibody.

The combined teachings of Ponath *et al.* and the Gordon *et al.* references, at best, would provide a method for treating ulcerative colitis by administering an antibody at a single dose of 3 mg/kg. If, for arguments sake only, the person of skill in the art was motivated to use the dose of 3 mg/kg as a starting point for optimizing treatment within the disclosed range, the results would still be unpredictable and require undue experimentation.

Indeed, further experimental data (Fedyk *et al.*, Reference AZ5 of record) addresses the Examiner's concerns regarding whether the antibody used in Feagan *et al.* (LDP-02) is actually preferable to natalizumab for treatment of ulcerative colitis. Two humanized antibodies, Humanized ACT-1 antibody, which binds α4β7-integrin heterodimer, and natalizumab, which binds molecules comprising α4-integrin, including α4β7-integrin and α4β1-integrin heterodimers, were compared in studies in non-human primates. As expected for the desired therapeutic effect, humanized ACT-1 antibody inhibited migration of lymphocytes to the gastrointestinal tract. However, not even high, multiple doses of humanized ACT-1 antibody could induce the systemic immunosuppression that was observed in primates treated with single, lower doses of natalizumab in these studies.

A separate, integrated safety analysis was performed on data from nine clinical trials in healthy subjects and patients with inflammatory bowel disease (IBD) (Feagen *et al.*, Reference AR6 of record). Overall 84% of subjects who received drug/treatment reported at least one adverse event (AE) compared to 87% placebo subjects. The Humanized ACT-1 Antibody was well-tolerated in all clinical trials to date with no increase in systemic infections and a possible trend in increased upper respiratory and mucosal infections.

Although other agents such as corticosteroids and TNF-α blockers may also be used to treat IBD in humans, the recited antibody is safer in comparison to these other treatments for IBD as well. Corticosteroids and TNF-α blockers also cause general immunosuppression outside of the GI tract and are associated with opportunistic infections (See Toruner *et al.*. Reference AS6 filed concurrently herewith; Hoentjen *et al.*, Reference AT6 filed concurrently herewith; Marehbian *et al.*, Reference AU6 filed concurrently herewith).

Thus, in addition to showing surprising results in treating inflammatory bowel disease with a dose of MoAb that is 2.0 mg/kg, further experimental data in support of the claimed invention has been generated by Applicants. In this regard, Applicants have demonstrated that LDP-02 in doses clearly higher than the 3 mg/kg disclosed in the prior art have improved safety over natulizumab. Natulizumab (Antegren) has been associated with an opportunistic infection of the brain, progressive multifocal leukoencephalopathy (PML), which is believed to be caused by impaired immune surveillance of the CNS.

Filed concurrently herewith is a Declaration of Eric Fedyk under 37 C.F.R. § 1.132, that describes nonclinical studies that demonstrate improved safety by vedolizumab (previously LDP-02, MLN02, MLN0002) compared to natulizumab. The Declaration describes nonclinical studies that were conducted by Millennium Pharmaceuticals, Inc., an assignee of the subject application. In the first nonclinical study, the potential effects of vedolizumab and natalizumab on the onset of experimental autoimmune encephalomyelitis (EAE) were investigated in Rhesus macaque. In a second nonclinical study, a head-to-head safety comparison of vedolizumab and natalizumab was performed.

In particular, the potential effects of vedolizumab (a humanized antibody to $\alpha 4\beta 7$ integrin that contains the six CDRs specified in claim 1) and natalizumab (Antegren) on the onset of experimental autoimmune encephalomyelitis (EAE) were investigated in Rhesus macaque. The animals received an initial intravenous bolus of vehicle control, 30 mg/kg natalizumab or 30mg/kg vedolizumab before subcutaneous immunization with recombinant human myelin/oligodendrocyte glycoprotein (rhMOG), and were dosed once weekly thereafter. The study concluded that vedolizumab does not impair immune surveillance of the CNS and thus, may have a lower risk of inducing PML than natalizumab. (Fedyk Declaration at paragraph 20.)

Vedolizumab was also shown not to affect organs and tissues outside of the gastrointestinal (GI) tract. (Fedyk Declaration at paragraph 36) Natalizumab is known to cause general immunosuppression outside of the gastrointestinal (GI) tract, which can produce an uncertain combination of unwanted systemic side effects. Such side effects decrease the benefit/risk ratio of natalizumab and can increase monitoring and management of patients with IBD. This study showed that vedolizumab does not affect organs and tissues outside of the GI tract.

As shown in the Declaration, vedolizumab has no effect on systemic adaptive immune responses, as measured by the T cell dependent antibody response (TDAR). In contrast, treatment with natalizumab caused increased spleen weights, induced hyperplasia, and significant inhibition of IgM TDAR. (Fedyk Declaration at paragraph 36.)

The nonclinical studies presented in the Declaration demonstrate improved safety over Antegren (natalizumab). Thus, in addition to the surprising results in treating IBD with a dose of vedolizumab that is lower than that used previously with natalizumab, Applicants have shown that vedolizumab in doses clearly higher than the 3 mg/kg disclosed in the prior art have improved safety over natalizumab. Accordingly, the invention is not obvious.

Reconsideration and withdrawal of the rejection are respectfully requested.

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

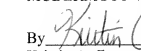
A Supplemental Information Disclosure Statement (SIDS) is being filed concurrently herewith. Acknowledgment of consideration of the references cited therein is respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

MCDERMOTT WILL & EMERY LLP

By 

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